

REMARKS

The specification and claims 13, 14, and 15 have been amended to correct an error of a typographical nature. In particular, the R¹² designation of Phe for PTR 3205 is a duplication of the R¹³ substituent and should not be present. This is clearly shown in Example 2, wherein the detailed synthesis of PTR 3205 is disclosed. By following this synthesis, the structure of PTR-3205 is correctly disclosed as:

Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3)-X

This sequence is known in the art to have the correct formula shown above (see Falb et al., "In situ generation of Fmoc-amino acid chlorides for extremely difficult couplings to sterically hindered secondary amines in solid phase peptides synthesis," Proceedings of the 16th American Peptide Symposium, June 26-July 1, 1999, a copy of which is enclosed).

Thus no new matter is introduced by these changes, so that their entry at this time is appropriate. The marked versions of the amendments to the specification are in Appendix A. The proposed amendments are shown on Appendix B, while a complete set of pending claims is presented in Appendix C.

No fee is believed to be due for this submission. Should any fees be required, please charge them to Winston & Strawn deposit account no. 501-814.

A new power of attorney is enclosed. Please direct all further communication to Customer No. 28765.

Respectfully submitted,

Date 8/20/01


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Enclosure

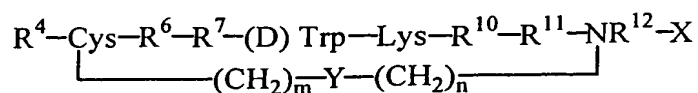
On page 7, please replace old Table 1 with the following new Table:

Table 3. The most preferred analogs.

PTR	Sequence
3171	Phe*-Phe-Phe-(D)Trp-(D)Lys-Phe(C2)-X
3113	Phe(C1)-Phe-Phe-(D)Trp-Lys-Phe(N2)-X
3123	Phe(C1)-Phe-Phe-(D)Trp-(D)Lys-Phe(N2)-X
3209	Phe(N2)-Tyr-(D)2Nal-Lys-Val-Gly(C2)-Thr-X
3183	Phe(N2)-Tyr-(D)Trp-Lys-Val-Gly(C2)-2Nal-X
3185	Phe(N2)-Tyr-(D)Trp-Lys-Val-Val-Gly(C2)-X
3201	Phe(N2)-Tyr-(D)Trp-Lys-Ser-2Nal-Gly(C2)-X
3203	Phe(N2)-Phe-(D)Trp-Lys-Thr-2Nal-Gly(C2)-X
3173	GABA*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X
3197	Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X
3205	Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-[Phe-]Phe(N3)-X
3207	(D)Phe-Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X
3229	Galactose-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X

On page 22, please replace the paragraph beginning with "Another preferred embodiment" with the following paragraph:

Another preferred embodiment has the general formula:



Formula No. 14

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R⁴ is (D)- or (L)-Phe or Tyr;

R⁶ is (D)- or (L)-Phe or Tyr;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)-1Nal or (D)- or (L)-2Nal, or

Tyr;

R¹⁰ is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

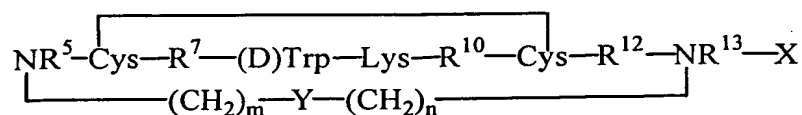
R¹¹ is (D)- or (L)-Phe or (D)- or (L)-Ala;

R¹² is Gly, Val, [or](D)- or (L)-Phe or is absent; and

Y² is thioether, thioester or disulfide.

Also on page 23, please replace the paragraph starting with "Another more preferred embodiment" with the following paragraph:

Another more preferred embodiment has the general formula:



Formula No. 15

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R⁵ is (D)- or (L)-Phe or (D)- or (L)-Ala;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal or (D)- or (L)- 2Nal, or Tyr;

R¹⁰ is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R¹² is Gly, Val, [or](D)- or (L)-Phe or is absent;

R¹³ is (D)- or (L)-Phe or (D)- or (L)-Ala; and

Y² is amide, thioether, thioester or disulfide.

Page 26, please replace old Table 3 with the following new Table 3:

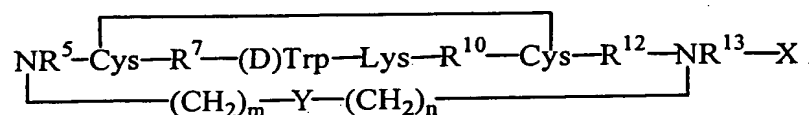
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PTR	Sequence
3171	Phe*-Phe-Phe-(D)Trp-(D)Lys-Phe(C2)-X
3113	Phe(C1)-Phe-Phe-(D)Trp-Lys-Phe(N2)-X
3123	Phe(C1)-Phe-Phe-(D)Trp-(D)Lys-Phe(N2)-X
3209	Phe(N2)-Tyr-(D)2Nal-Lys-Val-Gly(C2)-Thr-X
3183	Phe(N2)-Tyr-(D)Trp-Lys-Val-Gly(C2)-2Nal-X
3185	Phe(N2)-Tyr-(D)Trp-Lys-Val-Val-Gly(C2)-X
3201	Phe(N2)-Tyr-(D)Trp-Lys-Ser-2Nal-Gly(C2)-X

3203	Phe(N2)-Phe-(D)Trp-Lys-Thr-2Nal-Gly(C2)-X
3173	GABA*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X
3197	Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X
3205	Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-[Phe-]Phe(N3)-X
3207	(D)Phe-Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X
3229	Galactose-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X

APPENDIX B
MARKED VERSION OF THE CLAIMS THE CLAIMS

13. The backbone cyclized somatostatin analog of claim 1 having the general formula
 15:



Formula No. 15

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R⁵ is (D)- or (L)-Phe or (D)- or (L)-Ala;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal or (D)- or (L)- 2Nal, or Tyr;

R¹⁰ is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R¹² is Gly, Val, [or] (D)- or (L)-Phe, or is absent;

R¹³ is (D)- or (L)-Phe or (D)- or (L)-Ala; and

Y² is amide, thioether, thioester or disulfide.

14. The backbone cyclized somatostatin analog of claim 13 wherein:

R⁵ is Phe;

R⁷ is Phe;

R¹⁰ is Thr;

R¹² is Gly, Val, [or] (D)- or (L)-Phe, or is absent;

R¹³ is Phe; and

Y² is amide.

15. The backbone cyclized somatostatin analog of claim 1 having the formula:

Phe(N2)-Tyr-(D)2Nal-Lys-Val-Gly(C2)-Thr-X;
Phe(N2)-Tyr-(D)Trp-Lys-Val-Gly(C2)-2Nal-X;
Phe(N2)-Tyr-(D)Trp-Lys-Val-Val-Gly(C2)-X;
Phe(N2)-Tyr-(D)Trp-Lys-Ser-2Nal-Gly(C2)-X;
Phe(N2)-Phe-(D)Trp-Lys-Thr-2Nal-Gly(C2)-X;
GABA*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X;
Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X;
Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-[Phe-]Phe(N3)-X;
(D)Phe-Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X; or
Galactose-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X;

wherein X designates a terminal carboxy acid, amide, or alcohol group; the asterisk denotes that the bridging group is connected between the N^α-ω-functionalized derivative of an amino acid and the N-terminus of the peptide or the side chain of the Cys residue.

APPENDIX C
CLAIMS UPON ENTRY OF PRELIMINARY AMENDMENT

5 1. A backbone cyclized somatostatin analog that incorporates at least one building unit,
said building unit containing one nitrogen atom of the peptide backbone connected to a
bridging group comprising an amide, thioether, thioester, or disulfide, wherein the at least
one building unit is connected via the bridging group to form a cyclic structure with a
moiety selected from the group consisting of a second building unit, the side chain of an
10 amino acid residue of the sequence or the N-terminal amino acid residue.

15



20

Q is hydrogen or a mono- or di- saccharide

R⁶ is (D)- or (L)-Phe or Tyr;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)-1Nal, (D)- or (L)-2Nal, or Tyr;

R^8 is (D)- or (L)-Trp;

R⁹ is (D)- or (L)-Lys;

R^{10} is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R^{11} is (D)- or (L)-Phe, (D)- or (L)-Ala, Nle, or Cys; and

R^{12} is Gly, Val, Leu, (D)- or (L)-Phe, 1Nal, or 2Nal.

3. The backbone cyclized somatostatin analog of claim 2 wherein:

Q is hydrogen;

R^5 is GABA;

R⁶ is Phe;

R⁷ is Trp;

R⁸ is (D)-Trp;

R⁹ is Lys;

R¹⁰ is Thr;

R¹¹ is Phe;

5 R¹² is Gly;

n is 3; and

X is an amide.

4. The backbone cyclized somatostatin analog of claim 2 wherein:

10 Q is galactose;

R⁵ is Dab;

R⁶ is Phe;

R⁷ is (L)-Trp;

R⁸ is (D)-Trp;

15 R⁹ is Lys;

R¹⁰ is Thr;

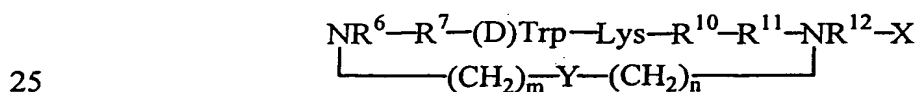
R¹¹ is Phe;

R¹² is Gly;

n is 3; and

20 X is an amide.

5. The backbone cyclized somatostatin analog of claim 1 having the general formula 8:



Formula No. 8

wherein: m and n are 1 to 5

X designates a terminal carboxy acid, amide or alcohol group;

30 R⁶ is (D)- or (L)-Phe, or (D)- or (L)-Ala;

R⁷ is Tyr, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R¹⁰ is Thr, Val, Ser, or Cys;

R¹¹ is Val, (D)- or (L)-1Nal, (D)- or (L)-2Nal, or (D) or (L)-Phe;

R¹² is Gly, (D)- or (L)-Ala, or (D) or (L)-Phe; and

35 Y² is amide, thioether, thioester or disulfide.

R⁶ is (D)- or (L)-Phe or Tyr;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal or (D)- or (L)- 2Nal, or Tyr;

R¹⁰ is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R¹¹ is (D)- or (L)-Phe or (D)- or (L)-Ala;

5 R¹² is Gly, Val, or (D)- or (L)-Phe; and

Y² is thioether, thioester or disulfide.

12. The backbone cyclized somatostatin analog of claim 11 wherein:

R⁴ is (D)Phe;

10 R⁶ is Phe;

R⁷ is Trp;

R¹⁰ is Thr;

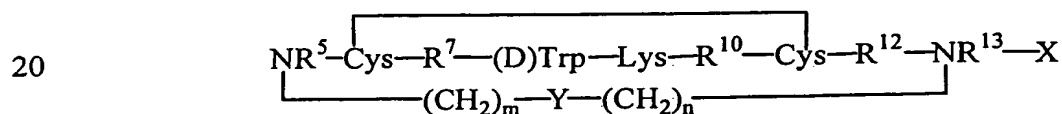
R¹¹ is Phe;

R¹² is Gly; and

15 Y² is disulfide.

13. The backbone cyclized somatostatin analog of claim 1 having the general formula

15:



Formula No. 15

wherein m and n are 1 to 5;

25 X designates a terminal carboxy acid, amide or alcohol group;

R⁵ is (D)- or (L)-Phe or (D)- or (L)-Ala;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal or (D)- or (L)- 2Nal, or Tyr;

R¹⁰ is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R¹² is Gly, Val, (D)- or (L)-Phe, or is absent;

30 R¹³ is (D)- or (L)-Phe or (D)- or (L)-Ala; and

Y² is amide, thioether, thioester or disulfide.

14. The backbone cyclized somatostatin analog of claim 13 wherein:

R⁵ is Phe;

35 R⁷ is Phe;

R¹⁰ is Thr;
R¹² is Gly, Val, (D)- or (L)-Phe, or is absent
R¹³ is Phe; and
Y² is amide.

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15. The backbone cyclized somatostatin analog of claim 1 having the formula:

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Phe(N2)-Tyr-(D)2Nal-Lys-Val-Gly(C2)-Thr-X;
Phe(N2)-Tyr-(D)Trp-Lys-Val-Gly(C2)-2Nal-X;
Phe(N2)-Tyr-(D)Trp-Lys-Val-Val-Gly(C2)-X;
Phe(N2)-Tyr-(D)Trp-Lys-Ser-2Nal-Gly(C2)-X;
Phe(N2)-Phe-(D)Trp-Lys-Thr-2Nal-Gly(C2)-X;
GABA*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X;
Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X;
Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3)-X
(D)Phe-Cys*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(S2)-X; or
Galactose-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-Gly(C3)-X;

15

wherein X designates a terminal carboxy acid, amide, or alcohol group; the asterisk denotes
20 that the bridging group is connected between the N^α-ω-functionalized derivative of an
amino acid and the N-terminus of the peptide or the side chain of the Cys residue.

16. A pharmaceutical composition comprising a backbone cyclized somatostatin analog
according to claim 1 and a pharmaceutically acceptable carrier.

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17. The composition according to claim 16 wherein the backbone cyclic analog is
selective for one somatostatin receptor subtypes.

18. The composition according to claim 16 wherein the backbone cyclic analog is
30 selective for two somatostatin receptor subtypes.

19. A method for treating disorders selected from the group consisting of
atherosclerosis, autoimmune diseases, cancers, diabetic-associated complications, endocrine
disorders, inflammation, gastrointestinal disorders, pancreatitis, post-surgical pain, and
35 restenosis comprising administering to a mammal in need thereof a pharmaceutical

composition comprising a therapeutically effective amount of a backbone cyclized somatostatin analog according to claim 1.

20. The method according to claim 19 wherein the backbone cyclic analog is selective
5 for one somatostatin receptor subtype.

21. The method according to claim 19 wherein the backbone cyclic analog is selective for two somatostatin receptor subtypes.

10 22. A method for diagnosing cancer comprising administration of a backbone cyclized somatostatin analog of claim 1.

23. The method according to claim 22 wherein the backbone cyclic analog is used for imaging the existence of metastases.

15 24. The method according to claim 22 wherein the backbone cyclic analog is labeled with a detectable probe.

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